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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,622	09/29/2004	Masakatsu Kawakami	Q83855	1024

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EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 06/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/509,622	KAWAKAMI, MASAKATSU	
	Examiner	Art Unit	
	Iqbal Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,8 and 11-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8 and 11-13* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

Claims 2, 8, and 11-13 are currently pending.

In response to a previous Office action, a non-final requirement (mailed on January 11, 2006), Applicants filed a response and amendment received on April 10, 2006. Applicant's amendment of claims 2, and 8, canceling Claims 3-7 and 9-10, and newly adding claims 11-13 has been entered. Claims 2, 8, and 11-13 are pending in the instant Office action and will be examined herein.

Applicants' arguments filed on 4/10/2006 have been fully considered and are not deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Priority

Acknowledgement is made of applicants claim for foreign priority JP2002-165612 of 6/6/2002 and JP2003-60749 of 3/7/2003.

Withdrawn-Specification Objection (Abstract)

Acknowledgement is made of receiving a new abstract and has been entered.

New-Claim Objections

Claim 11 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 13. When two claims in an application are duplicates or else are so close in content that they both

cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Appropriate correction is required.

New-Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 8 is indefinite and vague in the recitation "reactive oxygen species" which is unclear and confusing. Does "reactive oxygen species," mean superoxide ion or something else? Clarification is required.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 8 is indefinite and vague in the recitation "accelerate expression" which is unclear and confusing. Does "accelerate expression," mean "activate expression"?

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the present instance, claim 12 part (4) recites "judging whether or not -----" is vague, which is unclear as to what steps or procedures that are encompassed. Clarification is required.

Maintained - Claim Rejections - 35 U.S.C. § 112 (1)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Previous rejection of claim 8 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained and new claim 12 is rejected 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This rejection has been discussed at length in the previous office action mailed on 1/11/2006. It is maintained for the reasons of record and discussed below.

Claims 8 and 12 are directed to use of a genus of protein molecule expressed specifically in RA patients having 95% or more homology to SEQ ID NO: 2. The specification teaches the structure and function of only a single representative species of such proteins and does not contain any disclosure of the structure and function of all protein sequences expressed specifically in RA patients that are 95% identical to SEQ ID NO: 2. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the expression of said polypeptides in RA patients. The genus of protein, having 95% identity to SEQ ID NO: 2 is a large variable genus with the potentiality of encoding many different proteins and the specification fails to teach which if any of these beyond SEQ ID NO: 2 are expressed in RA patients and fails to show that, all such proteins are functionally similar to SEQ ID NO: 2 as well. Therefore, many structurally and functionally unrelated polypeptides are encompassed within the scope of these claims. Given this lack of description of representative species and functions encompassed by the methods of the claim, the specification fails to

sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Applicants argue that the specification discusses the homology of SEQ ID N0: 2 with other known polypeptides at the paragraph bridging pages 2 and 3 of the specification, as well as at the paragraph bridging pages 9 and 10 and requested examiner to consider the full disclosure of the present specification, which is sufficient to show that Applicants were in possession of the claimed genus. Applicants also argue that the Example 14 of the "REVISED INTERIM WRIWEN DESCRPTION GUIDELINES TRAINING MATERIALS" (pages 53-56 are attached hereto as available on the Patent Office web-site) stating that Example 14 indicates that the written description requirement may be satisfied for a variant having at least 95% homology where: the central sequence is exemplified, variants are contemplated, procedures for making modifications are routine in the art, and an assay for detecting activity of the protein is described. It is respectfully submitted that Example 14 of the Patent Office written description guidelines supports patentability of the present claims under Section 1 12. (See Examples 5-7 of the Specification, as well as pages 15-17).

Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 8 and 12. The examiner acknowledges the amendment to the claims 2, 8 and adding new claims 11-13 and canceling claim 9, but disagrees with the applicant's contention that the claimed invention is adequately described. Claim 8 is directed to use of a genus of protein molecule expressed specifically in RA patients having 95% or more homology to SEQ ID NO: 2. However, the main issue to satisfy the written description requirement is having clear picture of structure and function of the claimed genus. Applicants

fulfill the structural feature but it is not clear what the main function of the protein is and applicants do not explicitly recite the function in the claim and just merely stating that "expressed specifically in RA patients in no way imparts a functional limitation to the claims. The specification discloses only the polypeptide of SEQ ID NO: 2 to produce reactive oxygen species (ROS) and to activate expression of TNF-α or COX-2, which is insufficient to adequately describe the required functional feature of the genus of protein encompassed by the claim. Applicants arguments that the instant claims are analogous to Example 14 of the "REVISED INTERIM WRIWEN DESCRPTION GUIDELINES TRAINING MATERIALS", is not persuasive an Example 14 is not analogous to the instant claims because Example 14 clearly stated the structure and function of a protein i.e. 95% identical to SEQ ID NO: 3, which catalyzes the reaction of A => B, which is absent in the instant application. The instant application does not say clearly what the function of the protein is but merely say "expressed specifically in RA patients". Therefore, for the reasons above, the rejection is maintained.

Previous rejection of claim 8 under 35 U.S.C. 112, first paragraph, on enablement issue is maintained and newly adding claim 12 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide of SEQ ID NO: 2 and methods for screening for compounds which inhibit the activity of said polypeptide to produce reactive oxygen species (ROS), which activate expression of TNF-œ or COX-2, does not reasonably provide enablement for use of any polypeptide expressed specifically in RA patients and having 95% or more of homology to SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the

invention commensurate in scope with these claims. This previous rejection has been fully discussed at length in the previous office action mailed on 1/11/2006. It is maintained for the reasons of record and discussed below.

Claim 8 is so broad as to encompass methods for screening for compounds which inhibit the polypeptide of SEQ ID NO: 2 expressed specifically in RA patients and having 95% or more of homology to SEQ ID NO: 2. The scope of the methods claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the method claims. The scope of the claimed invention is very broad in the context of lack of functional feature of the polypeptide.

Applicants argue that the present specification provides ample guidance to practice the full invention without undue experimentation. The specification discusses the homology of SEQ ID NO: 2 with other known polypeptides at the paragraph bridging pages 2 and 3 of the specification, as well as at the paragraph bridging pages 9 and 10. Thus, suitable modifications to SEQ ID NO: 2 within the scope of the claims can be reasonably predicted. Further, the technique of mutagenesis itself was routine in the art as of the present Application's filing date. For example, the technique of mutagenesis was used in a routine manner in the following literature references (copies of which are attached to this Amendment). Applicants further argue that, at the time of filing the present application, a kit for site-directed mutagenesis TM site-directed mutagenesis kit (i.e. Quick-change was available from Stratagene) was available. Accordingly, it is submitted that the present claims can be practiced with only routine experimentation on the basis of the present specification.

Applicant's arguments have been fully considered but are not deemed persuasive to

overcome the rejection of claims 8 and 11-13 on enablement issue. The examiner acknowledges the amendment to the claims 8 and adding new claims by providing more limitation but disagrees with the applicant's contention that the scope of the claimed invention is adequately described. Claims 8 and 12 are directed to methods for screening for compounds which inhibit the polypeptide of SEQ ID NO: 2 expressed specifically in RA patients and having 95% or more of homology to SEQ ID NO: 2. The scope of the methods claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the method claims.

Applicants discuss a lot about sequence, structure, and mutation etc; however, none of the claims recite any evidence of any functional feature of the genus nor does the specification provide any evidence as to which of the enormous number of possible variants which could be produced by said mutagenesis methods, actually are expressed in RA patients. Applicant's claims are in fact limited to only those variants not to variants having 95% identity. Even assuming that applicant's interest is to include man-made variants (in which case the recitation of expressed specifically in RA patients is confusing); the instant claims would not be enabled as written. Applicants need to limit the claim invention by reciting specific function of the recited polypeptide which should be correlated with its structural feature, otherwise, one of ordinary skill in the art would not be able to practice the claim invention, which requires that one of ordinary skill in the art to know or be provided with guidance for making the full scope of polypeptide to be utilized for a method of screening substance capable of inhibiting activity of the polypeptide, however, the activity of the polypeptide is not in the amended claims and applicants do not explicitly discuss what the actual activity of the polypeptide is? Without such

guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. The specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without effecting polypeptide activity; (B) the general tolerance of polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any polypeptide residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

For all the reasons above, the examiner finds that amendment of claim 8 and new claims 11-13 and applicant's arguments does not describe the functional features of claimed genus encompassed by the claims in sufficient detail to overcome the rejection. The functional feature, which is required, is not specified in the claims. Therefore, for the reasons above, the rejection is maintained.

Withdrawn-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Previous rejection of Claim 2 under 35 U.S.C. 102(b) as being anticipated by Banfi et al. (GenBank Accession No. AF166328, "Homo sapiens NADPH oxidase homolog 1 long form

variant (NOH1) mRNA, alternatively spliced, complete cds" and "A mammalian H+ channel generated through alternative splicing of the NADPH oxidase homolog NOH-1", Science. 2000 Jan 7; 287(5450): 138-42, see IDS) is withdrawn by virtue of applicants arguments.

Applicants argue that as described in the specification, there is one amino acid difference between the sequence of the reference (AF166328) and the sequence of SEQ ID NO: 2. i.e. amino acid 173 of SEQ ID NO: 2 is valine, which is isoleucine in AF166328. Accordingly, SEQ ID NO: 2 is novel. Applicant's arguments fully considered and claim 2 rejection is withdrawn because SEQ ID NO: 2 is novel with regard to prior art.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Previous rejection of Claim 8 (claim 9 is cancelled) and newly adding claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Banfi et al. (GenBank Accession No. AF166328, "Homo sapiens NADPH oxidase homolog 1 long form variant (NOH1) mRNA, alternatively spliced, complete cds" and "A mammalian H+ channel generated through alternative splicing of the NADPH oxidase homolog NOH-1", Science. 2000 Jan 7; 287(5450): 138-42, see IDS) in view of Ostrakhovitch et al. (Oxidative stress in rheumatoid arthritis leukocytes: suppression by rutin and other antioxidants and chelators", Biochem Pharmacol. 2001 Sep 15; 62(6): 743-6, see IDS) is maintained. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 8 and 12 on obviousness issue.

Applicants argue that oxidative stress is based on a force to withdraw electrons, i.e., oxidation; on the other hand, acidic stress is based on a high concentration of hydrogen ions, i.e., strong acid. Thus. acidic stress and oxidative stress are different. Applicants also argue that Ostrakhovitch teaches oxidative stress of RA leukocytes, but does not teach acidic stress. Meanwhile, Banfi et al. (Science) teach 1) that a proton channel for excreting intracellular protons participates in a protective mechanism for acidic stress, but does not teach that the proton channel participates in oxidative stress, 2) there are various types of NADPH oxidase families, and these are expressed differently. Applicants furthermore, asserts that the present inventors

discovered that NOX-1b, which is an NADPH oxidase, is expressed specifically in the synovial cells of RA patients as compared with the synovial cells of healthy individuals, thus leading to the present invention. Applicant's arguments have been fully considered but are deemed persuasive to overcome the rejection of claim 8 and 12 for the following reasons:

As discussed previously, Banfi et al. clearly suggest that NOH1 is nothing but a NADPH oxidase homologue, which may play an important role in cellular defense against acidic stress or oxidative stress since NADPH oxidase is also known as an oxidative stress producing polypeptide that produce reactive oxygen species (ROS) such as superoxide ion. Similarly, Ostrakhovitch et al. teach oxidative stress in rheumatoid arthritis leukocytes, which develops due to the activation of NADPH oxidase followed by the accumulation of reactive oxygen species (ROS). Ostrakhovitch et al. also teach a method of identifying compounds, which inhibits oxidative stress and identified rutin, which is very effective against oxidative stress due to the rheumatoid arthritis.

Therefore, it would have been obvious to one of ordinary skill in the art to use the polypeptide of Banfi et al. which cause oxidative stress by producing ROS or superoxide ion as disclosed by Ostrakhovitch et al, to use in the method of Ostrakhovitch et al, to identify or screen compounds or substances for the treatment of rheumatoid arthritis or osteoarthritis. One ordinary skill in the art would have been motivated to identify an agent, which would inhibit NADPH oxidase or homologue in order to reduce ROS or TNF-α or COX-2 for treating rheumatoid arthritis or osteoarthritis. For the reasons above and as discussed previously, the rejection is maintained.

Conclusion

No claim is in condition for allowance.

Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution. **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury, Ph.D. whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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